Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Isolated high home systolic blood pressure in patients with type 2 diabetes is a prognostic factor for the development of diabetic nephropathy: KAMOGAWA-HBP study

Nobuko Kitagawa [a], Emi Ushigome [a,*], Toru Tanaka [b], Goji Hasegawa [c], Naoto Nakamura [d], Masayoshi Ohnishi [e], Sei Tsunoda [f], Hidetaka Ushigome [g], Isao Yokota [h], Noriyuki Kitagawa [i], Masahide Hamaguchi [a], Mai Asano [a], Masahiro Yamazaki [a], Michiaki Fukui [a]

[a] Department of Endocrinology and Metabolism, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan
[b] Department of Endocrinology and Metabolism, Kyoto First Red Cross Hospital, Kyoto, Japan
[c] Department of Endocrinology and Metabolism, Kyoto Second Red Cross Hospital, Kyoto, Japan
[d] Saiseikai Kyoto Hospital, Kyoto, Japan
[e] Department of Endocrinology and Metabolism, Osaka General Hospital of West Japan Railway Company, Osaka, Japan
[f] Nishijin Hospital, Kyoto, Japan
[g] Department of Organ Transplantation and General Surgery, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan
[h] Department of Biostatistics, Graduate School of Medicine, Hokkaido University, Hokkaido, Japan
[i] Kameoka Municipal Hospital, Kyoto, Japan

ARTICLE INFO

Article history:
Received 26 July 2019
Received in revised form
27 September 2019
Accepted 5 November 2019
Available online 8 November 2019

Keywords:
Isolated high home systolic blood pressure
Hypertension
Diabetic nephropathy
Type 2 diabetes
Cohort study

ABSTRACT

Background: Isolated high home systolic blood pressure (IH-HSBP) has been revealed to be correlated with cardiovascular disease and diabetic nephropathy, however, the prognostic significance of IH-HSBP with the development of diabetic nephropathy is unclear.
Methods: In this prospective 2-year cohort study of 477 patients with normoalbuminuria, we investigated the effect of IH-HSBP on the development of diabetic nephropathy defined by diabetic nephropathy advanced from normoalbuminuira to micro or macroalbuminuria.
Results: Among 477 patients, 67 patients showed the development of diabetic nephropathy. In the multivariate logistic regression analyses, IH-HSBP was prognostic factor for the development of nephropathy after adjusting for sex, age, duration of diabetes mellitus, body mass index, total cholesterol, hemoglobin A1c, creatinine, smoking habits and use of renin-angiotensin-aldosterone system inhibitors (odds ratio: 2.53, 95% confidence interval: 1.16–5.56, $p = 0.020$).
Conclusion: IH-HSBP in patients with type 2 diabetes with normoalbuminuria was prognostic factor for the development of diabetic nephropathy. We should pay more attention to IH-HSBP to prevent the development of diabetic nephropathy.

* Corresponding author at: Department of Endocrinology and Metabolism, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, 465, Kajii cho, Kamigyo-ku, Kyoto-city, Kyoto 621-8585, Japan.
E-mail address: emis@koto.kpu-m.ac.jp (E. Ushigome).

https://doi.org/10.1016/j.diabres.2019.107920
0168-8227/

1. Introduction

Isolated systolic hypertension (ISH) is defined that systolic blood pressure (SBP) is disproportionately high compared with diastolic blood pressure (DBP) [1]. In particular, SBP is elevated because of mechanical properties of large vessels such as a decrease in arterial compliance [2–4]. It is the most common hemodynamic form of hypertension in elderly patients [5]. In the previous studies, ISH was shown to be a risk factor for mortality of cardiovascular disease [6,7].

Home-measured blood pressure (HBP) control is essential to prevent diabetic complication [8], especially diabetic nephropathy [9]. Furthermore, development of diabetic nephropathy is a risk factor for cardiovascular events and mortality [10–12].

We assumed that ISH assessed by HBP (home ISH), plays an important role in the development of diabetic nephropathy. However, no reports provided the relationship between ISH and diabetic nephropathy in patients with diabetes. The aim of the current study is to examine whether home ISH have a prognostic significance on the development of diabetic nephropathy in patients with type 2 diabetes.

2. Materials and methods

2.1. Study design

We used the same resources in our previous study work, which is based on data from the HBP cohort of type 2 diabetes patients who had regularly attended the diabetes outpatient clinic at the Kyoto Prefectural University of Medicine Hospital or other general hospitals located in the Kansai area in Japan (KAMOGAWA-HBP study) [13].

We evaluated the prognostic significance of HBP for the development of diabetic nephropathy in patients with type 2 diabetes. Nephropathy was graded as follows: normoalbuminuria, urinary albumin/creatinine ratio (UACR) less than 30 mg per gram of creatinine (mg/g Cr); microalbuminuria, 30–300 mg/g Cr; or macroalbuminuria, more than 300 mg/g Cr [14]. We defined the development of diabetic nephropathy when the stage of diabetic nephropathy advanced from normoalbuminuira to micro or macroalbuminuria during the two years. All methods of the present study were approved by the local Research Ethics Committee and were conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from every patient.

2.2. Data collection

We took blood samples for biochemical measurements in the morning. Serum lipid profile (triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol), creatinine, hemoglobin $A1_C$ (HbA1c), and other biochemical data were determined by standard laboratory measurements. UACR was measured with an immunoturbidimetric assay. A mean value for UACR was determined from three urinary measurements. HbA1c was used as National Glycohemoglobin Standardization Program unit as recommended by the Japan Diabetes Society [15]. Patient's data, including sex, age, duration of diabetes, smoking and alcohol drinking status and antihypertensive medication were obtained concurrently with HBP measurements. Neuropathy was defined by the diagnostic criteria for diabetic neuropathy proposed by Diagnostic Neuropathy Study Group [16]. In simple terms, it is essential that the absence of peripheral neuropathies other than diabetic neuropathy in diabetic patients. Furthermore, diabetic neuropathy is defined as two or more abnormalities among three neurological examination items: the presence of sensory symptom caused by diabetic neuropathy, decreased or absent Achilles tendon reflex (bilateral) and decreased vibratory sensation on bilateral medial malleolus diagnosed by a C128 Hz tuning fork. We defined macrovascular complication as having a medical history of cardiovascular disease, cerebrovascular disease or arteriosclerosis obliterans in the past. Alcohol drinking status (everyday, social or never) and smoking status (current, past or never) were assessed by interview.

2.3. HBP measurements

We instructed the patients to perform triplicate morning and evening BP measurements for 14 consecutive days, and calculated mean of the three measurements per morning and three per evening each day.

We classified BP categories as normal HBP (morning SBP < 125 mmHg and morning DBP < 75 mmHg), isolated high home SBP (IH-HSBP; morning SBP ≧ 125 mmHg and morning DBP < 75 mmHg), isolated high home DBP (IH-HDBP; morning SBP < 125 mmHg and morning DBP ≧ 75 mmHg), and high HBP; morning SBP ≧ 125 mmHg and morning DBP ≧ 75 mmHg) [17].

We indicated patients that measurements of morning BP were made within 1 h of awakening, before breakfast or taking any drugs, with seated and rested for at least 5 min [18]. The evening measurements of BP was obtained in the same methods before going to bed. The cuff was placed around the patient's non-dominant arm and the position of the cuff was maintained at the level of the heart. HBP measurements were executed using an automatic device, HEM-70801C (Omron Healthcare Co. Ltd, Kyoto, Japan), which uses the cuff-oscillometric method to generate a digital display of SBP/DBP values and heart rate. HEM-70801C uses the same components and BP determining algorithm to those of another device, HEM-705IT, which was previously validated and satisfied the criteria of the British Hypertension Society protocol [19].

2.4. Statistical analysis

Baseline characteristics were summarized by median with interquartile range or numbers. Logistic regression analyses were used to investigate the relationship between the development of diabetic nephropathy and IH-HSBP, IH-HDBP and high HBP, using normal HBP as a reference group. To adjust

the effects of various factors on the development of diabetic nephropathy, the following factors, which were known risk factors for the development of diabetic nephropathy, were considered as covariates: sex, age, duration of diabetes, body mass index, total cholesterol, hemoglobin $A1_C$, creatinine, smoking habits and use of antihypertensive medication (Model 2), and additional adjustment for use of renin-angiotensin-aldosterone system inhibitors instead of use of antihypertensive medications (Model 3).

Moreover, we performed the subgroup analyses. Subgroup factors were age (equal to or more than 65 years old and less than 65 years old) and use of antihypertensive drugs (the presence and the absence of antihypertensive medication). *P* values <0.05 were considered statistically significant. The statistical analyses were performed using the JMP version 13.2 software (SAS Institute Inc., Cary, NC, USA).

3. Results

HBP monitoring program recruited 1414 consecutive patients with type 2 diabetes, aged between 20 and 90. Sixty-four patients were excluded since insufficient data on HBP values, and 439 patients were also excluded whose data of UACR were not available. In addition, 121 patients who were newly prescribed with angiotensin II receptor blocker (ARB) or angiotensin-converting-enzyme inhibitor (ACE-I) or stopped with them during follow-up, 313 patients who were diagnosed with microalbuminuria or macroalbuminuria were also excluded. Finally, 477 patients with normoalbuminuria comprised the study population (Fig. 1). The diagnosis of type 2 diabetes was according to the American Diabetes Association criteria [20].

Among 477 patients with normoalbuminuria at baseline, 66 patients developed to microalbuminuria and 1 patient to macroalbuminuria after 2 years.

Clinical characteristics of patients are shown in Table 1. Median (interquartile range) age, duration of diabetes, BMI, total cholesterol and hemoglobin A_{1C} was 64.0 (59.0–71.0) years, 9.0 (4.0–15.0) years, 23.2 (21.4–25.5) kg/m^2, 189 (168–210) mg/dL and 7.0 (6.6–7.6) %, respectively. The unadjusted odds ratio (95% CI) of IH-HSBP, IH-HDBP and high HBP, using normal HBP as a reference group for the development of diabetic nephropathy was 3.27 (1.64–6.53), 0.30 (0.04–2.32), and 1.74 (0.88–3.42), respectively (Table 2). In the multivariable logistic regression analyses, IH-HSBP was also associated with the development of nephropathy in Model 2 (OR: 2.63, 95% CI: 1.20–5.76, $p = 0.016$), and in Model 3 (OR: 2.53, 95% CI: 1.16–5.56, $p = 0.020$) (Table 2).

We have performed the subgroup analyses according to the presence or absence of antihypertensive medications. In patients with antihypertensive medications, the adjusted odds ratio (95% CI) of IH-HSBP, using normal HBP as a reference group for the development of diabetic nephropathy, was 6.16 (1.38–27.54) (Table 3). In patients without antihypertensive medications, the adjusted odds ratio (95% CI) of IH-HSBP was 2.73 (0.58–12.80) (Table 3).

We have also performed the subgroup analyses by age. In patients with equal to or more than 65 years old, the adjusted odds ratio (95% CI) of IH-HSBP, using normal HBP as a reference group for the development of diabetic nephropathy, was 3.32 (1.14–9.65) (Table 4). In patients with less than 65 years old, the adjusted odds ratio (95% CI) of IH-HSBP, was 3.00 (0.62–14.44) (Table 4).

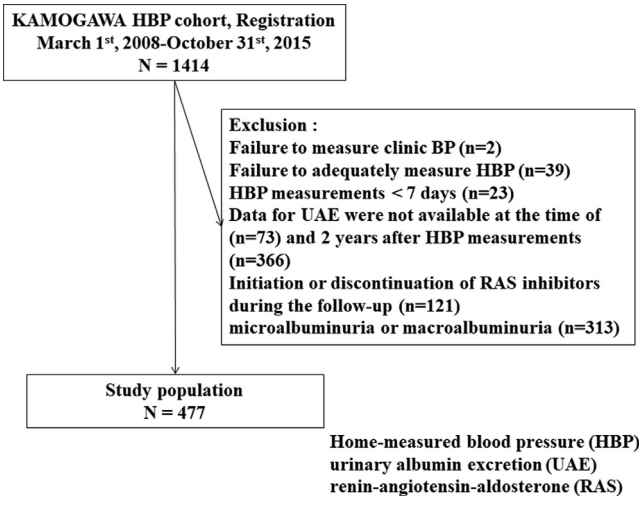

Fig. 1 – Study flow diagram for the registration of patients.

4. Discussion

IH-HSBP independently predicted the development of diabetic nephropathy after adjustment for potential confounders including sex, age, duration of diabetes mellitus, body mass index, total cholesterol, hemoglobin A1c, creatinine, smoking habits and use of antihypertensive medications in patients with type 2 diabetes. Previous studies revealed that elevated HBP in patients with diabetes was a risk factor for target organ dysfunction [21]. We previously reported that elevated HBP in patients with diabetes was associated with increased diabetic nephropathy [22]. Furthermore, patients with diabetic nephropathy have high coronary events compared with non-diabetic patients [23]. Therefore, preventing the development of diabetic nephropathy can lead to a reduction of patients who need to be treated for coronary heart disease.

The close mechanism how IH-HSBP makes progress in diabetic nephropathy is still unclear. The possible common mechanism between IH-HSBP and the development of diabetic nephropathy might be arterial aging [24,25]. Sixty to ninety percents of older adults tend to rise SBP with age [26], and more than sixty percents of older people with hypertension have ISH [27]. ISH is a result of reduced elasticity and compliance of large arteries and atherosclerosis [28,29]. Furthermore, ISH is a consequence of increased aortic stiffness and reduced aortic diameter, which lead to mismatch between pressure and flow and consequently increase the forward wave amplitude, contribute to high SBP [30]. Thus, ISH may be indicative of an early clinical stage of hyperdynamic circulation preceding the development of increased peripheral vascular resistance [31,32]. Previous studies suggested that high SBP may interact with an impaired kidney function to augment its deleterious effect on the cardiovascu-

Table 1 – Characteristics of patients.

Male/female	252/225
Age (y)	64.0 (59.0–71.0)
Duration of diabetes (y)	9.0 (4.0–15.0)
Body mass index (kg/m^2)	23.2 (21.4–25.5)
Mean morning systolic blood pressure (mmHg)	128.8 (117.2–137.8)
Mean morning diastolic blood pressure (mmHg)	72.7 (66.5–79.6)
Mean evening systolic blood pressure (mmHg)	123.4 (115.1–133.3)
Mean evening diastolic blood pressure (mmHg)	67.7 (61.8–73.9)
Clinic systolic blood pressure (mmHg)	135 (123.7–145.3)
Clinic diastolic blood pressure (mmHg)	76.3 (69.3–83.7)
Hemoglobin A1c (%)	7.0 (6.6–7.6)
Hemoglobin A1c (mmol/mol)	52.0 (48.6–59.5)
Total cholesterol (mg/dL)	189 (168–210)
Triglycerides (mg/dL)	109 (80–156)
Creatinine (mg/dL)	0.70 (0.59–0.83)
Smoking (never/previous/current)	258/125/65
Drinking (everyday/social/never)	96/92/263
Retinopathy (NDR/SDR/pre PDR, PDR)	353/61/33
Neuropathy (-/+)	360/110
Macrovascular complication (-/+)	385/86
Antihypertensive medication (-/+)	247/230

For categorical variables, n (%) is presented. For continuous variables, median (interquartile range) is presented. NDR, no diabetic retinopathy; SDR, simple diabetic retinopathy; PDR, proliferative diabetic retinopathy; RAS, renin-angiotensin-aldosterone system.

Table 2 – Unadjusted and adjusted odds ratios for the development of diabetic nephropathy.

Hypertension status (n)	Model 1		*Model 2		**Model 3	
	Unadjusted OR (95%CI)	*P* Value	Adjusted OR (95%CI)	*P* Value	Adjusted OR (95%CI)	*P* Value
Normal HBP group (166)	1		1		1	
Isolated high HSBP group (106)	3.27 (1.64–6.53)	0.001	2.63 (1.20–5.76)	0.016	2.53 (1.16–5.56)	0.020
Isolated high HDBP group (35)	0.30 (0.04–2.32)	0.246	0.45 (0.06–3.68)	0.457	0.49 (0.06–3.98)	0.503
High HBP group (170)	1.74 (0.88–3.42)	0.112	1.81 (0.83–3.94)	0.133	1.79 (0.82–3.89)	0.142

HBP, home-measured blood pressure; HSBP, home systolic blood pressure.

* Model 2: Odds ratios were adjusted for sex, age, duration of diabetes mellitus, body mass index, hemoglobin A_{1C}, total cholesterol, creatinine, smoking habits and use of antihypertensive medications.

** Model 3: Odds ratios were adjusted for variables in model 2 and additional adjustment for use of renin angiotensin system inhibitors instead of use of antihypertensive medications.

lar system [33]. Aortic stiffness is associated with incident albuminuria and the rate of decline in glomerular filtration rate in patients with type 2 diabetes [34].

Several studies have reported that the serum levels of advanced glycation end products (AGEs) are elevated in the patients with high SBP compared to DBP [35-37]. Additionally, It has also been indicated that age-related vascular changes would be accelerated by AGEs in patients with diabetic nephropathy [38,39]. Therefore, AGEs might be involved in the development of diabetic nephropathy by ISH. AGEs deposition can occur in the arterial wall, as largely on collagen causing pathological cross-linking [40]. In addition, AGEs may contribute to an increased collagen content in arterial walls, and promote arterial stiffness [41]. Moreover, nitric oxide (NO) dysregulation may lead to arterial stiffness and activate sympathetic nerve [42], which leads elevated SBP [43]. NO level is known to decrease in patients with diabetic nephropathy [44]. By these mechanisms, AGEs deposition and a decrease in production of NO might lead to the association of IH-HSBP with the development of diabetic nephropathy.

In subgroup analyses according to the presence or absence of antihypertensive medication, IH-HSBP in patients with antihypertensive medication was a prognostic factor for the development of nephropathy, whereas, those without antihypertensive medication was not. In our study, 223 (46.8%) patients were treated with antihypertensive medication. Despite of the medication, HSBP in patients with antihypertensive medication was higher than that in patients without (132.78 mmHg vs 123.76 mmHg, $P < 0.0001$), and the crude proportion of the development of nephropathy in patients with antihypertensive medication was also larger than that without (20.0% vs 8.5%, $P = 0.0003$). Therefore, the association between IH-HSBP and the development of nephropathy in

Table 3 – Unadjusted and adjusted odds ratios for the development of diabetic nephropathy in patients with and without antihypertensive medications.

Hypertension status (n)	Model 1		*Model 2	
	Unadjusted OR (95%CI)	*P* Value	Adjusted OR (95%CI)	*P* Value
With antihypertensive medication (n = 230)				
Normal HBP group (60)	1	1	1	
Isolated high HSBP group (62)	3.98 (1.46–10.83)	0.007	6.16 (1.38–27.54)	0.017
Without antihypertensive medication (n = 247)				
Normal HBP group (106)	1	1	1	
Isolated high HSBP group (44)	2.04 (0.71–5.87)	0.187	2.73 (0.58–12.80)	0.203

HBP, home-measured blood pressure; HSBP, home systolic blood pressure.
* Model 2: Odds ratios were adjusted for sex, age, duration of diabetes mellitus, body mass index, hemoglobin A_{1C}, total cholesterol, creatinine, smoking habits.

Table 4 – Unadjusted and adjusted odds ratios for the development of diabetic nephropathy in patients equal to or more than 65 years old and less than 65 years old.

Hypertension status (n)	Model 1		*Model 2		**Model 3	
	Unadjusted OR (95%CI)	*P* Value	Adjusted OR (95%CI)	*P* Value	Adjusted OR (95%CI)	*P* Value
≧65 years old (n = 235)						
Normal HBP group (77)	1		1		1	
Isolated high HSBP group (78)	2.63 (1.15–6.02)	0.022	3.33 (1.14–9.69)	0.028	3.32 (1.14–9.65)	0.028
<65 years old (n = 242)						
Normal HBP group (89)	1		1		1	
Isolated high HSBP group (28)	2.80 (0.70–11.25)	0.147	3.60 (0.75–17.37)	0.111	3.00 (0.62–14.44)	0.171

HBP, home-measured blood pressure; HSBP, home systolic blood pressure.
* Model 2: Odds ratios were adjusted for sex, age, duration of diabetes mellitus, body mass index, hemoglobin A_{1C}, total cholesterol, creatinine, smoking habits and use of antihypertensive medications.
** Model 3: Odds ratios were adjusted for variables in model 2 and additional adjustment for use of renin angiotensin system inhibitors instead of use of antihypertensive medications.

patients without antihypertensive medication might be weaker, compared to that in patients with antihypertensive medication.

In age-specific analysis, IH-HSBP in patients aged 65 or more was positively associated with the development of nephropathy, whereas, those under 65 years old was not. One of the possible reasons of this result is that mean of SBP in patients aged 65 or more was higher than that in patients under 65 years old (130.57 mmHg vs 125.72 mmHg, $P = 0.0005$). Furthermore, in the group of aged 65 or more, the proportion of patients with development of nephropathy were also larger than in the group under 65 years old (20.43% vs 7.85%, $P < 0.0001$). Therefore, the association between IH-HSBP and the development of nephropathy in patients under 65 years old might be weaker, compared to that in patients aged 65 or more.

Our study has several limitations. First, the length of our study was relatively short-term, therefore, the statistical power might be limited. Second, high salt intake could lead to increase in BP and peripheral vascular resistance [45]. In addition, most patients with diabetes may have salt sensitive hypertension. Therefore, salt restriction could result in stronger effects of reducing prevalence of hypertension as well as diabetic nephropathy [46]. However, we did not have the data of them. Third, protein intake is also associated with developing of diabetic nephropathy [47]. In addition, there is also evidence showing the beneficial effects of exercise in diabetic nephropathy [33]. However, we did not have the data of them. If we had the data, we could more clearly identify the prognostic significance of HBP for the development of diabetic nephropathy.

In conclusion, we demonstrated, for the first time, that IH-HSBP in patients with type 2 diabetes was a prognostic factor for the development of diabetic nephropathy in this prospective 2-year cohort study. Therefore, we should focus more on IH-HSBP to predict and prevent the development of diabetic nephropathy.

Author contributions

N.K. designed the study, performed data analyses and reviewed/edited the manuscript. E.U. designed the study, contributed to the collection of research data, performed data analyses, drafted the manuscript, and was the main study physician responsible for the KAMOGAWA-HBP study in Kyoto Prefectural University of Medicine, Graduate School of Medical Science. S. M. and C.O. designed the study protocol, reviewed data reports, and reviewed the study manuscript.

T.T. was the principal investigator of the Kyoto First Red Cross Hospital. G.H. was the principal investigator of the Kyoto Second Red Cross Hospital. M.O. was the principal investigator of the Osaka General Hospital of West Japan Railway Company. H.U. designed the study protocol, reviewed data reports, contributed to discussion, and reviewed the study manuscript. I. Y. supervised data analysis, contributed to manuscript preparation, contributed to discussion, and reviewed/edited the manuscript. N.N. designed the study protocol, reviewed data reports, and reviewed the study manuscript. M.F. designed the protocol, performed data analyses, drafted the manuscript, and was the principal investigator of the Kyoto Prefectural University of Medicine, Graduate School of Medical Science and lead principal investigator for the study. All authors reviewed and provided edits and comments on manuscript drafts. N.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments

The authors acknowledge Dr. Atsushi Omoto and Dr. Wataru Fukuda of Kyoto First Red Cross Hospital, Dr. Shin-ichi Mogami and Dr. Yoshihiro Kitagawa of Osaka General Hospital of West Japan Railway Company and Dr. Yohei Oda of Social insurance Kyoto Hospital, for their assistance of collecting data. We thank Naoko Higo R.N., Machiko Hasegawa R.N., and Terumi Kaneko R.N. of the Kyoto Prefectural University of Medicine, for teaching patients how to measure their blood pressure and Sayoko Horibe, Hiroko Kawamura and Aiko Aida also of the Kyoto Prefectural University of Medicine, for their secretarial assistance.

Declaration of Competing Interest

N. K., E. U., S. M., C. O., M. T., M. Y., N. N., and M. F. have received grant and research support from AstraZeneca plc, Astellas Pharma Inc., Bristol-Myers Squibb K.K., Daiichi Sankyo Co., Ltd., Eli Lilly Japan K.K., Kyowa Hakko Kirin Company Ltd., Kowa Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Corp., Novo Nordisk Pharma Ltd., Nippon Chemiphar Company Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Sanofi K.K., Taisho Toyama Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and TERUMO Co. For the remaining authors were non-declared. The sponsors were not involved in the study design; in the collection, analysis, interpretation of data; nor in the writing of this manuscript; nor in the decision to submit the article for publication. The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article. The authors declare that although they are affiliated with a department that is supported financially by pharmaceutical company, the authors received no current funding for this study and department affiliation does not alter their adherence to all journal policies on sharing data and materials. E. U. received grant support from the Japanese Study Group for Physiology and Management of Blood Pressure and the Astellas Foundation for Research on Metabolic Disorders (grant number: 4024).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107920.

REFERENCES

[1] Fletcher AE, Bulpitt CJ. Isolated systolic hypertension in the elderly. Cardiovasc Risk Fact 1992;2:133–9.
[2] Byyny RL. Hypertension in the elderly. In: Laragh JH, Brenner BM, editors. Hypertension. Pathophysiology, diagnosis, and management. New York: Raven Press; 1995. p. 227–51.
[3] Lakatta EG. Mechanism of hypertension in the elderly. J Am Geriatr Soc 1989;7:780–90.
[4] Messerli FH, Ventura H, Aristimuno GG, Suarez DH, Dreslinski GR, et al. Arterial compliance in systolic hypertension. Clin Exper Hypertens 1982;A4:1037–44.
[5] Bavishi C, Goel S, Messerli FH. Isolated systolic hypertension: an update after SPRINT. Am J Med 2016;129(12):1251–8.
[6] Antikainen R, Jousilahti P, Tuomilehto J. Systolic blood pressure, isolated systolic hypertension and risk of coronary heart disease, strokes, cardiovascular disease and all-cause mortality in the middle-aged population. J Hypertens 1998;16 (5):577–83.
[7] Tsimploulis A, Sheriff HM, Lam PH, Dooley DJ, Anker MS, et al. Systolic-diastolic hypertension versus isolated systolic hypertension and incident heart failure in older adults: insights from the Cardiovascular Health Study. Int J Cardiology 2017;15(235):11–6.
[8] Eguchi K. Blood pressure management in patients with type 2 diabetes. Intern Med 2015;54(18):2285–9.
[9] Ushigome E, Oyabu C, Tanaka T, Hasegawa G, Ohnishi M, et al. Impact of masked hypertension on diabetic nephropathy in patients with type II diabetes: a KAMOGAWA-HBP study. J Am Soc Hypertens 2018;12(5):364–71.
[10] Gerstein HC, Mann J, Yi Q, Zinman B, Dinneen SF, et al. Albuminuria and risk of cardiovascular events, death, and heart failure. JAMA 2001;286:421–6.
[11] Kramer H, Jacobs DR, Bild D, Post W, Saad MF, et al. Urine albumin excretion and subclinical cardiovascular disease: the multi-ethnic study of atherosclerosis. Hypertension 2005;46:38–43.
[12] Krolewski AS, Niewczas MA, Skupien J, Gohda T, Smiles A, et al. Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria. Diabetes Care 2014;37:226–34.
[13] Ushigome E, Fukui M, Sakabe K, Tanaka M, Inada S, et al. Uncontrolled home blood pressure in the morning is associated with nephropathy in Japanese type 2 diabetes. Heart Vessels 2011;26:609–15.
[14] Nakade Y, Toyama T, Furuichi K, Kitajima S, Miyajima Y, et al. Impact of kidney function and urinary protein excretion on intima–media thickness in Japanese patients with type 2 diabetes. Clin Exp Nephrol 2015;19:909–17.
[15] Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, et al. International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diabetes Investig 2012;3(1):39–40.

[16] Yasuda H, Sanada M, Kitada K, Kitajima S, Miyajima Y, et al. Rationale and usefulness of newly devised abbreviated diagnostic criteria and staging for diabetic polyneuropathy. Diabetes Res Clin Pract 2007;77:S178–83.
[17] Kai H. Blood pressure management in patients with type 2 diabetes mellitus. Hypertens Res 2017;40(8):721–9.
[18] Imai Y, Otsuka K, Kawano Y, Shimada K, Hayashi H, et al. Japanese Society of Hypertension (2003) Japanese Society of Hypertension (JSH) guidelines for self-monitoring of blood pressure at home. Hypertens Res 2003;26:771–82.
[19] Coleman A, Fraaman P, Steel S, Shennan A. Validation of the Omron 705IT (HEM-759-E) oscillometric blood pressure monitoring device according to the British Hypertension Society protocol. Blood Press Monit 2006;11(1):27–32.
[20] The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2002;25:S5–S20.
[21] Kamoi K, Miyakoshi M, Soda S, Kaneko S, Nakagawa O. Usefulness of home blood pressure measurement in the morning in type 2 diabetic patients. Diabetes Care 2002;25 (12):2218–23.
[22] Ushigome E, Hamaguchi M, Matsumoto S, Oyabu C, Omoto A. Optimal home SBP targets for preventing the progression of diabetic nephropathy in patients with type 2 diabetes mellitus. J Hypertens 2015;33(9):1853–9. discussion 1859.
[23] Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach Alberta Kidney Disease Network S. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet 2012;380:807–14.
[24] Lee HY, Oh BH. Aging and arterial stiffness. Circ J 2010;74 (11):2257–62.
[25] Ford ML, Tomlinson LA, Chapman TP, Rajkumar C, Holt SG. Aortic stiffness is independently associated with rate of renal function decline in chronic kidney disease stages 3 and 4. Hypertension 2010;55(5):1110–5.
[26] Fagard RH. Epidemiology of hypertension in the elderly. Am J Geriatr Cardiol 2002;11:23–8.
[27] Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995;25:305–13.
[28] Franklin SS, Gustin 4th W, Wong ND, Larson MG, Weber MA. Hemodynamic patterns of age-related changes in blood pressure. The Framingham heart study. Circulation. 1997;96:308–15.
[29] Safar ME. Arterial aging–hemodynamic changes and therapeutic options. Nat Rev Cardiol 2010;7:442–9.
[30] Mitchell GF, Conlin PR, Dunlap ME, Lacourcière Y, Arnold JM, et al. Aortic diameter, wall stiffness, and wave reflection in systolic hypertension. Hypertension 2008;51 (1):105–11.
[31] Messerli FH, Frohlich ED, Suarez DH, Reisin E, Dreslinski GR, et al. Borderline hypertension: relationship between age, hemodynamics and circulating catecholamines. Circulation 1981;648(4):760–4.
[32] Julius S, Pascual AV, London R. Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension. Circulation 1971;44:413–8.
[33] Ekundayo OJ, Allman RM, Sanders PW, Aban I, Love TE, et al. Isolated systolic hypertension and incident heart failure in older adults: a propensity-matched study. Hypertension 2009;53(3):458–65.
[34] Bouchi R, Babazono T, Mugishima M, Yoshida N, Nyumura I, et al. Arterial stiffness is associated with incident albuminuria and decreased glomerular filtration rate in type 2 diabetic patients. Diabetes Care 2011;34:2570–5.
[35] Semba RD, Najjar SS, Sun K, Lakatta EG, Ferrucci L. Serum carboxymethyl-lysine, an advanced glycation end product, is associated with increased aortic pulse wave velocity in adults. Am J Hypertens 2009;22(1):74–9.
[36] Semba RD, Sun K, Schwartz AV, Varadhan R, Harris TB, et al. Serum carboxymethyl-lysine, an advanced glycation end product, is associated with arterial stiffness in older adults. J Hypertens 2015;33(4):797–803.
[37] Prasad K, Mishra M. Do advanced glycation end products and its receptor play a role in pathophysiology of hypertension?. Int J Angiol 2017;26(1):1–11.
[38] Sell DR, Monnier VM. Molecular basis of arterial stiffening: role of glycation a mini-review. Gerontology 2012;58 (3):227–37.
[39] Chawla D, Bansal S, Benerjee BD, Madhu SV, Kalra OP, et al. Role of advanced glycation end product (AGE)-induced receptor (RAGE) expression in diabetic vascular complications. Microvasc Res 2014;95:1–6.
[40] Powell JT, Vine N, Crossman M. On the accumulation of D-aspartate in elastin and other proteins of the ageing aorta. Atherosclerosis 1992;97(2–3):201–8.
[41] Schnider SL, Kohn RR. Effects of age and diabetes mellitus on the solubility and nonenzymatic glucosylation of human skin collagen. J Clin Invest 1981;67(6):1630–5.
[42] Brillante DG, O'Sullivan AJ, Johnstone MT, Howes LG. Arterial stiffness and hemodynamic response to vasoactive medication in subjects with hemodynamic response to vasoactive medication in subjects with insulin-resistance syndrome. Clin Sci (Lond) 2008;114(2):139–47.
[43] Young CN, Fisher JP, Gallagher KM, Whaley-Connell A, Chaudhary K, et al. Inhibition of nitric oxide synthase evokes central sympatho-excitation in healthy humans. J Physiol 2009;587:4977–86.
[44] Prabhakar S, Starnes J, Shi S, Lonis B, Tran R. Diabetic nephropathy is associated with oxidative stress and decreased renal nitric oxide production. J Am Soc Nephrol 2007;18:2945–52.
[45] Ha SK. Dietary salt intake and hypertension. Electrolyte Blood Press 2014;12:7–18.
[46] Machnik A, Neuhofer W, Jantsch J, Dahlmann A, Tammela T, et al. Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. Nat Med 2009;15(5):545–52.
[47] Zhu HG, Jiang ZS, Gong PY, Zhang DM, Zou ZW, et al. Efficacy of low-protein diet for diabetic nephropathy: a systematic review of randomized controlled trials. Lipids Health Dis 2018;17(1):141.